REMARKS

Entry of the foregoing amendments is respectfully requested.

Summary of Amendments

Upon entry of the foregoing amendments, claims 18, 31 and 32 are cancelled, claims 17 and 19 are amended and claims 37-39 are added, whereby claims 17, 19-30 and 33-39 will be pending, with claims 17, 26 and 37 being independent claims. Support for the new claims can be found throughout the present specification and in the original claims.

Applicants emphasize that the amendment to independent claim 17 is without prejudice or disclaimer, and Applicants expressly reserve the right to prosecute claim 17 in its original, unamended form in one or more continuation and/or divisional applications.

Summary of Office Action

As an initial matter, Applicants note with appreciation that the Examiner has withdrawn the rejections under 35 U.S.C. § 35 U.S.C. § 112, first paragraph, and 35 U.S.C. § 103(a) set forth in the previous Office Action and has withdrawn the finality of the previous Office Action.

Claims 17-21 and 26-27 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly not providing reasonable enablement for the treatment of any and all allergic

diseases caused by HRF and any and all benzimidazole compounds and for the treatment without any specified endpoint.

Claims 17-36 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over a newly cited document, i.e., Hamaguchi et al., Int. Arch. Allergy Immunology 2001; 126(4), pp. 318-324 (hereafter "HAMAGUCHI"), in view of U.S. Patent No. 6,491,943 (hereafter "TSUJI"),

Response to Office Action

Withdrawal of the rejections of record is respectfully requested, in view of the foregoing amendments and the following remarks.

Response to Rejection of Claims under 35 U.S.C. § 112, First Paragraph

Claims 17-21 and 26-27 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method of treating certain allergic diseases, allegedly does not reasonably provide enablement for the treatment of all allergic diseases caused by HRF with any and all benzimidazole compounds and for the treatment without any specified endpoint. In this regard, the Examiner carries out an analysis of the *Wands* factors and concludes that in view of the breath of the claims, the chemical nature of the invention, the unpredictability of the art, and the lack of working examples regarding the activity as claimed one skilled in the art allegedly would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

Applicants respectfully traverse this rejection for various reasons. In particular, Applicants do not understand the allegations in the last paragraph of page 3 of the present Office Action according to which "the invention ... has not recited the step(s) that (a) result in preventing nor (b) have a specified end result of the treatment." Clarification is respectfully requested.

At any rate, Applicants respectfully submit that the present claims do not recite a prevention of an allergic disease. Also, it is not seen why there has to be a specified end result of the treatment. It would appear that it is evident to one of ordinary skill in the art that any noticeable alleviation of the symptoms of an allergic disease qualifies as "treatment" of the allergic disease in the sense of the present claims. In this regard, also the Examples of the present application may be referred to. Merely as an example, in the passage following the table at page 18 of the present specification it is stated that "it was found that in the groups treated with the inventive composition, symptoms of allergic rhinitis were remarkably reduced as compared to the positive control group. As a result, it can be found that the inventive composition can effectively reduce allergic diseases, including allergic rhinitis and hay fever." This statement clearly indicates and confirms that a reduction of the symptoms of an allergic disease is a "treatment" within the meaning of this term in the present claims.

Regarding the breath of the present claims, Applicants respectfully submit that all of the present independent claims recite specific compounds for use in the inhibition of the secretion of HRF and the treatment of allergic diseases, respectively. Additionally, all of the independent claims recite that the specific compounds have proton pump

inhibitor activity and, in the case of claims 17 and 37, that these compounds comprise lipid-soluble weak bases.

Regarding the comments in passage 3) at page 4 of the present Office Action, Applicants submit that U.S. Patent No. 6,861,425 to Ito et al. relied on by the Examiner for supporting the allegation that "the ability of treating of [sic] any and all allergic diseases caused by HRF with any and all benzimidazole compounds is not yet known in the art" discloses benzimidazole compounds which are structurally significantly different from the benzimidazole compounds of the present invention.

At any rate, it is not seen that the fact that the benzimidazole compounds of Ito et al. are useful as analgesics is an indication, or even evidence, that any of the benzimidazole compounds used in the methods of the present invention (having proton pump inhibitor activity) is not effective in the treatment of any allergic disease. Applicants point out that the Examiner has not provided any documentary evidence which would allow one to conclude that any of the benzimidazole compounds recited in the present claims is unsuitable for the treatment of any allergic disease.

In this regard, Applicants also respectfully request clarification regarding the "unpredictability of preventing caner" mentioned at page 5, line 8 from the bottom of the present Office Action.

Regarding the direction and guidance provided by the present specification, it is submitted that the present application contains several working examples which illustrate the administration of the compounds used in the present invention to human patients and to animals (mice) and the (favorable) results obtained thereby.

Applicants further point out that regarding the 7th and 8th *Wands* factors, which factors are not addressed in the present Office Action, the relative skill of those skilled in the art is high and the state of the prior art is such that even without any working examples, one of ordinary skill in the art would have no problems to successfully make and use the present invention.

Applicants submit that for at least all of the foregoing reasons, the rejection of claims 17-21 and 26-27 under 35 U.S.C. § 112, first paragraph, is unwarranted and should be withdrawn, which action is respectfully requested.

Response to Rejection of Claims under 35 U.S.C. § 103(a)

Claims 17-36 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over HAMAGUCHI, in view of TSUJI. The rejection essentially asserts that HAMAGUCHI teaches the use of a benzimidazole compound, i.e., TU-572, for the treatment of allergies such as anaphylaxis and urticaria via a reduction of IgE. In this regard, the Examiner appears to be of the opinion that TU-572 is similar in structure to the compounds recited in, e.g., present claim 17. TSUJI is alleged to teach in col. 2, lines 14-16 thereof that catechins suppress histamine release and can also treat allergies via a reduction of IgE, wherefore there would allegedly have been motivation to combine HAMAGUCHI with TSUJI.

Applicants respectfully traverse this rejection as well. First, it is not clear to Applicants why the rejection relies on TSUJI, and Applicants respectfully request clarification in this regard.

Second, Applicants note that HAMAGUCHI, while describing a single benzimidazole derivative, i.e., TU-572, which may be useful in the treatment of allergic diseases such as anaphylaxis and urticaria, clearly teaches that the effect of TU-572 is based on a mechanism, i.e., specific inhibition of CD45 (PTPase), which is completely different from the effect on which the present claims are based, i.e., inhibition of the secretion of IgE-dependent HRF by benzimidazole compounds with proton pump inhibitor activity.

HAMAGUCHI does not contain any indication that TU-572 exhibits proton pump inhibitor activity, nor does HAMAGUCHI teach or suggest that any benzimidazole compounds different from TU-572 have an activity similar to that of the latter. On the contrary, on page 320, middle of left column, of HAMAGUCHI it is indicated that several benzimidazole derivatives were synthesized, but only TU-572 exhibited potent and specific inhibitory effects with respect to CD45.

Accordingly, even if one were to disregard the difference in the mechanism of action between TU-572 and the compounds recited in the present claims, HAMAGUCHI does not teach or suggest that any benzimidazole derivative different from TU-572 shows beneficial effects with respect to the treatment of allergies such as anaphylaxis and urticaria. TSUIJ does not cure the deficiencies of HAMAGUCHI in that it does not even relate to benzimidazole derivatives.

Specifically, HAMAGUCHI teaches that TU-572 exhibits an anti-allergic effect because it inhibits *tyrosine PTPase (Protein-Tyrosine-Phosphatase)*. Neither HAMAGUCHI nor any other documents published up to the present that Applicants are

aware of teach or suggest that TU-572 has proton pump inhibitor activity. Further, Applicants are not aware that CD45 inhibition or similar physiological effects have ever been reported for compounds such as omeprazole and any of the other benzimidazole proton pump inhibitors recited in the present claims.

HAMAGUCHI performed experiments based on the theory that "*inhibition of CD45*" plays an important role in the anti-allergic effect. HAMAGUCHI found TU-572 through a high-throughput screening system in the course of a search for a compound having CD45 inhibitory activity, which compound happened to be a benzimidazole compound. In comparison, Applicants found that certain benzimidazoles having proton pump inhibitor activity such as, e.g., omeprazole, significantly reduce the release of HRF in the course of a search for compounds which can "*prevent the release of IgE-dependent HRF*". This further illustrates the fact that HAMAGUCHI has nothing to do with the present invention and is unable to teach or suggest same.

According to TSUJI, the histamine-release inhibitory effect of catechin is because of its inhibitory effect on the influx of calcium ions into cells or the *phosphorylation of the tyrosine residue* of certain proteins which play an important role in the histamine release process, i.e., not because catechin exhibits proton pump inhibitory activity. Accordingly, the disclosure of TSUJI that certain green tea catechins suppress histamine release and can treat allergies has nothing to do with the present invention.

Also, TSUJI fails to describe the precise histamine inhibitory mechanism of catechin. Further, the significant structural difference between catechins and

benzimidazoles would have been another disincentive for one of ordinary skill in the art to combine HAMAGUCHI and TSUJI.

IgE-dependent histamine releasing factor (HRF) secreted from the immune cells such as macrophages binds with receptors on the cells like basophils and stimulates secretion of histamine, IL-3, IL-13, etc. which cause an immune response. Accordingly, the benzimidazoles having proton pump inhibitor activity used in the methods of the present invention inhibit the secretion of HRF and thereby indirectly, i.e., as a result of the inhibition of the secretion of HRF, also inhibit the secretion of histamine, IL-3, IL-13, etc. and eventually exhibit an anti-allergic effect. In comparison, both TU-572 and catechin are reported to directly inhibit the secretion of histamine (i.e. not via the inhibition of the secretion of HRF), which appears to be related to the phosphorylation of tyrosine (i.e., not to the secretion of HRF). That is, the compounds of the present invention can block an allergic reaction at an earlier stage than TU-572 and catechin can, which makes the method of the present invention more potent and efficient.

To sum up, considering the fact that the anti-allergic effect of TU-572 or catechin is due to reasons different from the inhibition of the secretion of HRF and that the inhibition of the secretion of HRF by proton pump inhibitors such as, e.g., omeprazole is neither taught nor suggested by the cited documents (and the prior art that Applicants are aware of in general), HAMAGUCHI and TSUJI, alone or in combination, are unable to render obvious the subject matter of any of the claims submitted herewith.

For at least all of the foregoing reasons, the rejection of present claims 17-36 under 35 U.S.C. § 103(a) over HAMAGUCHI in view of TSUJI is without merit, wherefore withdrawal thereof is warranted and respectfully requested.

CONCLUSION

In view of the foregoing, it is believed that all of the claims in this application are in condition for allowance, which action is respectfully requested. If any issues yet remain which can be resolved by a telephone conference, the Examiner is respectfully invited to contact the undersigned at the telephone number below.

Respectfully Submitted,
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